Increased Risk of Cardiovascular Disease in Young Women Following Gestational Diabetes Mellitus

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OBJECTIVE — To determine whether women with gestational diabetes mellitus (GDM) have an increased risk of cardiovascular disease (CVD) following pregnancy.

RESEARCH DESIGN AND METHODS — All women aged 20–49 years with live births between April 1994 and March 1997 in Ontario, Canada, were identified. Women with GDM were matched with 10 women without GDM and were followed for CVD.

RESULTS — The matched cohorts included 8,191 women with GDM and 81,262 women without GDM. Mean age at entry was 31 years, and median follow-up was 11.5 years. The hazard ratio for CVD events was 1.71 (95% CI 1.08–2.69). After adjustment for subsequent type 2 diabetes, the hazard ratio was attenuated (1.13 [95% CI 0.67–1.89]).

CONCLUSIONS — Young women with GDM had a substantially increased risk for CVD compared with women without GDM. Much of this increased risk was attributable to subsequent development of type 2 diabetes.

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Gestational diabetes mellitus (GDM) is a common condition affecting 2–4% of pregnant women (1) and is associated with adverse outcomes for both the fetus and the mother. Previous GDM is a major risk factor for type 2 diabetes, which occurs in 20–60% of affected women within 5 years of the pregnancy (2). Women with a history of GDM are also at increased risk of other cardiovascular risk factors, such as obesity, hypertension, dyslipidemia, and the metabolic syndrome (3–5), as well as subclinical atherosclerosis (6). Taken together, these findings suggest that GDM identifies a population of young women at increased risk for cardiovascular disease (CVD). We used population-based administrative data to determine whether women with GDM have a heightened risk for CVD compared with women without GDM and whether any increase in risk is independent of subsequent type 2 diabetes.

RESEARCH DESIGN AND METHODS

— We conducted a population-based retrospective cohort study using administrative databases from Ontario, Canada, that included hospital discharge abstracts, physician service claims, and demographic data. The Ontario Diabetes Database is a validated registry of physician-diagnosed nongestational diabetes that is identified using these administrative data (7). Individuals are linked between all data sources via a unique health card number, which is reproducibly encrypted in all of these data sources.

Women aged 20–49 years who had a hospitalization record indicating a live birth between April 1994 and March 1997 were selected. For women who had more than one birth during this period, one birth was selected at random. Those who had pregestational diabetes or a CVD event (as defined below) in the prior 3 years were excluded.

Baseline characteristics were age at delivery, region of residence, and socioeconomic status (measured as the neighborhood income quintile). Subjects with missing data were excluded. Women were defined as having GDM using an algorithm analogous to that used by the validated registry to exclude GDM: one hospitalization record or two ambulatory physician claims bearing the diagnosis of diabetes or GDM between 120 days before and 180 days after delivery.

The primary outcome (CVD events) was defined as a hospitalization for acute myocardial infarction, stroke, coronary artery bypass, coronary angioplasty, or carotid endarterectomy. The prespecified secondary outcome (coronary artery disease [CAD] events) was hospitalization for acute myocardial infarction, coronary artery bypass, or coronary angioplasty. Subsequent diagnosis with diabetes was identified if the woman entered the diabetes registry postpartum. Although the registry does not distinguish between types, the majority of women developing diabetes in this group would have type 2 diabetes. All women were followed until March 2007, with censoring on death.

Subjects with GDM were matched with 10 subjects without GDM based on baseline characteristics. Kaplan-Meier survival curves were constructed for both outcomes. Cox proportional hazards regression was used to model the association of GDM with each outcome, accounting for the matched design of the study. For each outcome, an unadjusted model and a model adjusting for subsequent diagnosis of diabetes as a time-dependent covariate were built. The assumption of proportionality was verified by plotting log(–log[survival]) versus log(time) to assess parallelism. The study was approved by the institutional review board of Sunnybrook Health Sciences Centre.

RESULTS

— There were 356,891 potentially eligible women with live births during the study period. However, 3,127 were excluded because of preexisting diabetes, and 43 were excluded because of previous CVD. A further 2,036 were

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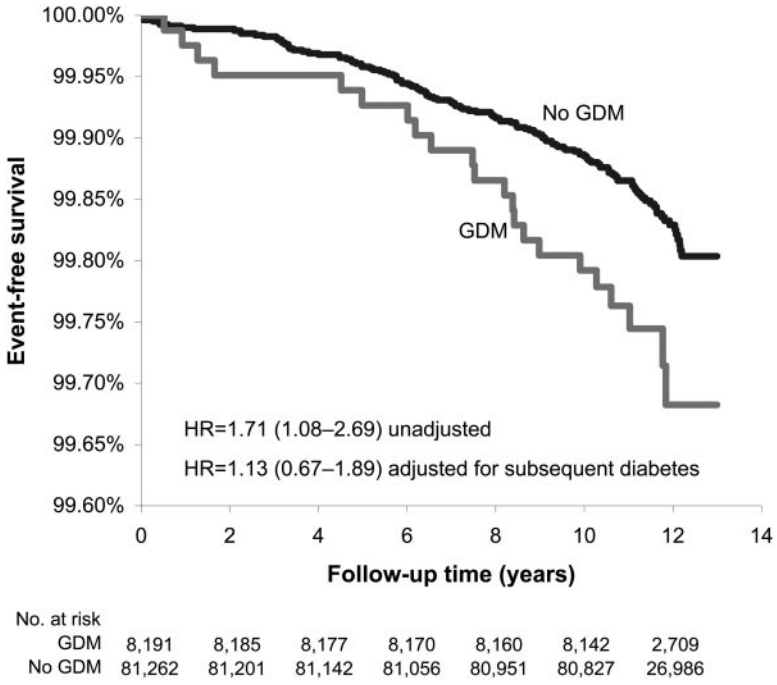

Figure 1—*Kaplan-Meier survival curves for CVD and CAD events and hazard ratios (HRs) derived from Cox proportional hazards regression.*

excluded due to missing data, mostly socioeconomic status. Of the remaining 351,685 subjects, 8,194 (2.3%) had GDM during the index pregnancy. The matched cohorts included 8,191 women with GDM and 81,262 without GDM. The mean age of both cohorts was 31 years.

The median follow-up time was 11.5 years. Diabetes developed during follow-up in 2,214 (27.0%) of the women with GDM and 2,596 (3.2%) of the women without GDM. Event-free survival for both CVD and CAD events are plotted in Fig. 1. Significant associations were found between GDM and both outcomes, but these associations were attenuated following adjustment for subsequent diabetes.

CONCLUSIONS — Our study is the first of its kind to show that young women with GDM have a substantially increased risk for CVD relative to women without GDM. The subsequent development of type 2 diabetes accounts for much of this increased risk, which reinforces the vital need for diabetes prevention strategies in this high-risk population.

Our findings are consistent with a cross-sectional study conducted by Carr et al. (5), which reported that women with a history of GDM had odds ratios for CVD and CAD similar to those reported here (1.85 and 1.58, respectively). However, this study was cross-sectional and relied on retrospective self-report to ascertain exposures and outcomes. In contrast, our cohort study used a more rigorous end point assessment and followed a much larger population of women over many years.

Our study used administrative data where clinical information, such as cardiovascular risk factors, was unavailable. Women with GDM exhibit chronic insulin resistance (8), which is associated with a clustering of risk factors that are in the causal pathway to CVD. Therefore, women with GDM likely have very different risk factor profiles than those without GDM, and adjusting for these differences might obscure a clinically important association between GDM and CVD.

In summary, women with GDM are at increased risk for CVD events compared with women without GDM, and much of this risk is attributable to the subsequent development of type 2 diabetes. As diabetes prevention interventions in women with a history of GDM have also been shown to slow progression of atherosclerosis (9), this study highlights the importance of diabetes prevention for this high-risk population.

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